

REMARKS

The Applicant now responds to the Office Action (“Action”) of July 29, 2006.

Applicant has amended claim 28 to more properly reflect antecedent basis. Support for this amendment may be found, for example, in original claim 21 as well as at paragraphs [0001] and [0023] of the Specification. Applicant has also amended claim 31 to depend from claim 30, instead of claim 21, to similarly reflect more proper antecedent basis. Support for this amendment may be found, for example, at claim 30. Finally, Applicant has added new claim 46, which finds support, for example, at paragraphs [0001], [0010], [0023], and [0030] of the Specification. No other amendments have been made, and no new matter is added to the claims. Thus, with this amendment, claims 21, 28-35, 41-43 and 46 are pending for examination.

Petition to Correct Inventorship

Applicant thanks the Office for considering and entering Applicant’s petition to correct inventorship under 37 CFR 1.48(b) and for acknowledging the removal of the Kelly patent, U.S. Patent No. 6,340,703, as a reference.

§ 112 Rejections of Claims 28 and 31

The Office rejects claims 28 and 31 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Specifically, the Office rejects claim 28 for insufficient antecedent basis for the limitation “treatment or prevention of osteoporosis” in lines 1-2. *See* Action at 2. Further, the Office rejects claim 31 for insufficient antecedent basis for the limitation “said dosage form” in line 1. *See id.*

Solely to facilitate prosecution, Applicant has amended claim 28 to recite:

Claim 28 (amended). A method according to claim 21 for the ~~treatment or prevention of osteoporosis~~ beneficial alteration or maintenance of bone density.

Support for this amendment may be found in at least paragraphs [0001] and [0023] of the Specification. Further, Applicant has amended claim 31 to depend from claim 30 instead of from claim 21. Support for this amendment may be found, for example, at claim 30.

With these amendments, Applicant respectfully requests the Office to withdraw the rejection of claims 28 and 31 under 35 U.S.C. § 112, second paragraph.

§ 103(a) Rejection of Claims 21, 28-35, and 41-43

The Office continues to reject claims 21, 28-35 and 41-43 under 35 U.S.C. § 103(a) as being unpatentable over Kelly WO 93/23069 (Kelly '069) in view of Empie et al. 6,261,565 B1 ("Empie"). Applicant respectfully traverses and seeks in this paper to address certain misapprehensions of the teachings of the references on which the continued rejections rely.

First, the Office urges that "it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods and compositions of Kelly '069 for use in treating osteoporosis, because in view of Empie et al.'s teachings, one of ordinary skill in the art would reasonably expect the *substantially similar isoflavone containing compositions of Kelly '069* to be effective in treating such disorders." Action at 4 (emphasis added). In fact, the compositions of Kelly '069 are "not substantially similar isoflavone containing compositions." As set forth in detail in the Amendment filed on May 16, 2006, the Kelly '069 compositions do not have high proportions of formononetin. Instead, the Kelly '069 compositions need not even include formononetin, as emphasized by the italics in the following:

- According to the "Disclosure of Invention," the supplement is "specifically enriched for isoflavones *selected from* genistein, daidzein, formononetin, and biochanin A." [Specification at 8].

- The ratio of genistein (and/or its derivative biochanin A) to daidzein (*and/or* its derivative formononetin) is between 1:2 to 2:1. [*Id.*].
- It is affirmatively “unimportant” whether the Kelly ‘069 compositions include either the methylated formononetin or the demethylated diazein, as follows:

It is thought that because the methyl forms (biochanin A and formononetin) ultimately are largely demethylated to their principles, genistein and daidzein, with improved biological efficacy, then it is *unimportant whether the isoflavones are present in the claimed product in methylated or demethylated forms*. [Specification at 10, paragraph 2]

- It is affirmatively suggested that genistien and daidzein be present in equal proportions, as follows:

Given that the relative biological importance of the two isoflavones groups (being genistein and daidzein) to human health remain unclear, and that each might indeed have different importance, plus the fact that both isoflavones are present in the diet in approximately equal proportions, then *it is prudent that both isoflavones be present in the claimed product in approximately equal proportions*. [*Id.* at 10, paragraph 1]

Thus, Kelly ‘069 does not provide “substantially similar isoflavone containing compositions.”

Also in drawing the conclusion of obviousness, the Office relies on Empie’s teaching that “isoflavones are known to be useful in treating osteoporosis.” Action at 4. However, as is well established, the references must be read as a whole, MPEP § 2141.03 at 2100-132, and, when taken as a whole, Empie’s teaching is not as applicable as the Office believes. While Empie does indicate the use of isoflavones for osteoporosis, Empie also notes that lignans may be used to prevent osteoporosis (col. 2, lines 36-38). In Example 1, Empie notes again the alleviation of osteoporosis by both isoflavones or lignans but goes on to attribute this to their estrogenic activity, as follows:

Isoflavones or lignans can alleviate menopausal-related symptoms, such as hot flashes and osteroporosis, as well as alleviate

symptoms associated with menstruation. This is further believed to be due to their estrogenic activity. [Col. 7, lines 5-8]

And Kelly '069 teaches at page 9, paragraph 5, that although additional studies should be done on estrogenic activity, formononetin is the least estrogenic of the isoflavones genistein, biochanin A, equol, and daidzein. When these statements are considered together, the two references suggest that the more estrogenic isoflavones genistein, biochanin A, equol, and daidzein would be more useful than the less estrogenic formononetin in alleviating osteoporosis.

Finally, in making the rejection as well as in responding to Applicant's prior arguments that both Kelly '069 and Empie teach away from high proportions of formononetin, the Office states that "with respect to the claimed ratios, since Kelly '069 and Empie et al. have established that *the therapeutic efficacy of the isoflavones is dependent upon their ratio amounts*, it would have been obvious to one of ordinary skill in the art to further modify the methods and compositions of Kelly and Empie et al. such that the isoflavones are present in a ratio that is effective to optimize their therapeutic activity." Action at 5 and 6-7 (emphasis added).

Neither reference, however, demonstrates that the therapeutic efficacy of the isoflavones is dependent upon their ratio amounts. In fact, the only explicit discussion of a ratio in Kelly '069 did not tie that ratio to any level of efficacy. As noted above, the "Disclosure of Invention" states that:

It is also preferred that the ratio of genistein **and/or** its methylated derivative biochanin A to daidzein **and/or** its methylated derivative formononetin is between 1:2 to 2:1.

(Specification at 8, paragraph 2) (emphasis added). Elsewhere, the specification indicates that it was "prudent" to provide genistein and daidzein in "approximately equal proportions." Specification at 10, paragraph 3. In discussing the use of the invention "for the prophylaxis or

treatment of a human, to combat conditions associated with phyto-estrogen deficiency,” the specification suggests the inclusion of

[G]enistein, **and/or** biochanin A, **and/or** daidzein, **and/or** formononetin.

Id. at 16, paragraph 1, last sentence (emphasis added). Finally, none of the examples compared the therapeutic efficacy of any ratios of isoflavone. Example 4 did demonstrate that the administration of soy hypocotyls which contained 45 mg of daidzein and 5 mg of genistein had beneficial effects on cholesterol levels, benign breast disease and irregular menstruation, but that ratio of daidzein to genistein was not compared with any other amount. And of course, as noted above, the specification indicated that it was “unimportant” whether the composition even contained the methylated isoflavones formononetin and biochanin A.

Empie similarly does not suggest that the therapeutic efficacy is dependent upon a ratio of isoflavones. Empie does, as the Office noted, discuss a ratio of the derivatives of genistein (and/or its precursor biochanin) to derivatives of daidzein (and/or its precursor formononetin) of from 100:1 to 1:100, but that range merely covers the entire spectrum. Moreover, there are no comparative tests, let alone any discussion, that a particular ratio corresponds to a certain level of efficacy. Example 4 and Table 4 do present a comparison of known products to the “improved composition” of the invention and that table does note the genistein/daidzein ratio as a point of comparison, but the only discussion relates to the increased amount of isoflavone glycosides (and saponins), not the effect of the ratio. And none of the isoflavone-based compositions made in Examples 1-4 even indicate the amounts or ratios of the specific isoflavones. The separate solutions in Example 5 were made merely to test solubility and do not even include one based on formononetin.

Thus, neither Kelly '069 nor Empie suggests, let alone establishes, that the therapeutic efficacy is dependent upon ratio amounts. As a consequence, neither reference can suggest that the ratio is an aspect to be optimized, let alone that the ratio is a "result effective variable." For at least this reason, the Office's reliance on the decisions of *Aller*, *Antonie*, and *Giesler* is misplaced.

Specifically, the Office asserted that:

Moreover, the court has held "it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 105 USPQ 233, 235 (CCPA 1955). Only if "the results of optimizing a variable are 'unexpectedly good' can a patent be obtained for a claimed critical range." *In re Antonie*, 195 USPQ 6, 8 (CCPA 1977). See also *In re Geisler*, 43 USPQ2d 1362 (CAFC 1997). Therefore the Examiner respectfully submits, in view of Empie and Kelly '069 disclosure, and absent evidence of unexpected results, it would have been prima facie obviousness to arrive at the claimed ratios. Action at 7.

As an initial and historical matter, the Office is correct that *Aller* "set out the rule that the discovery of an optimum value of a variable in a known process is normally obvious." See *Antonie* at 620. But the facts in *Aller* demonstrate that it is not applicable to this case and, as the CCPA later recognized in *Antonie*, there are also exceptions to that rule.

First, as to the facts in *Aller*, the process that appellants sought to patent was identical to that in the prior art, "except that appellants' claims specif[ied] lower temperatures and higher sulphuric acid concentrations than are shown in the reference." *Aller*, 105 U.S.P.Q. at 234. In affirming the rejection, the CCPA noted that appellants had not shown anything "critical" about their process. *Id.* at 236. In upholding the decision of the Board of Appeals, the Court relied on a portion of the Board's opinion:

...any one in possession of the information presented by [the prior art] would naturally experiment to discover optimum conditions of temperature and concentration of acid for commercial exploitation of the process. Such experimentation is no more than the

application of the expected skill of the chemical engineer and failure to perform such experiments would, in our opinion, show a want of the expected skill of the engineer. *Id.* at 237.

In the instant case, unlike in *Aller*, the claimed invention is not identical to that of the prior art, because the prior art does not teach high proportions of formononetin. *See* Kelly '069 at page 8 and at page 10, paragraphs 2 and 3; *see also* Empie at Col. 4, lines 16-18, and lines 44-47 and Col. 7, lines 4-5.

Moreover, unlike *Aller*, Applicant has demonstrated the unexpected benefit of high proportions of formononetin. First, the health benefits found with a composition containing a high formononetin content is highly unexpected and surprising because it was generally believed in the prior art that any beneficial effect of isoflavones on the bone was associated with an estrogenic effect, and formononetin displays the weakest estrogenic function of genistein, daidzein, formononetin, and biochanin. *See* Specification at page 10, lines 23-30. Second, it was assumed that formononetin should have equivalent function to daidzein, as the human body demethylates formononetin to daidzein. *See id.* As to the demonstration of the value of high proportions of formononetin, Example 4 shows that postmenopausal who received an isoflavone enriched with formononetin, particularly at 50 mg, "showed a highly significant and positive effect on cortical bone density (proximal forearm) in the first six months (4.1% increase)." *Id.* at 25. Thus, the basic rule of *Aller* is simply not applicable to the claimed invention.

Moreover, *In re Antonie* stands for a far more fundamental proposition than relied upon by the Office. Not only does it acknowledge that there are exceptions to the *Aller* rule, but it also provides a specific exception, i.e., where the prior art has not recognized the "result-effective" capability of a particular invention parameter. *Antonie*, 559 F.2d at 620. Indeed, the CCPA noted that recognition of the importance of the parameter is "essential" to the obviousness of

experiments on the parameter. Thus, where the “parameter optimized was not recognized to be a result-effective variable,” *Aller* does not apply. *Id.* As set forth in detail above, neither reference establishes that the therapeutic efficacy is dependent upon the ratio amount. Accordingly, neither reference has established that the ratio of isoflavones is a result-effective variable.

Applicant also notes that *Antonie* teaches that the standard for obviousness is what the reference, *as a whole*, actually teaches, not whether it “would be obvious for one of ordinary skill in the art to try varying every parameter of a system in order to optimize the effectiveness of the system even if there is no evidence in the record that the prior art recognized that particular parameter affected the result.” *Antonie*, 559 F.2d at 619-620.

Lastly, the Federal Circuit’s decision in *Geisler* is not applicable here. It merely restates and applies the basic proposition of *Aller*, as confirmed in *Antonie*, but does not address the exception to *Aller* established in *Antonie*. It is that exception, the failure of the art to recognize a result-effective variable, that the Office may have overlooked in the present case.

Accordingly, the cited references do not render the claimed invention obvious. Far from providing compositions that are “substantially similar,” Kelly ‘069 affirmatively teaches away from high proportions of formononetin. Empie’s suggestion that isoflavones can be used to treat osteoporosis would not be broadly applied to compositions high in formononetin but low in the more estrogenic isoflavones. And neither reference suggests, let alone demonstrates, that the therapeutic efficacy of isoflavones is dependent upon their ratio amounts. The mere optimization cases are simply not applicable to the present case where there is no recognition of a “result-effective variable.” For at least these reasons, the surprising and unexpectedly good results obtained with high formononetin warrant allowance of the pending claims.

CONCLUSION

With the entry of this Amendment, claims 21, 28-35, 41-43 and 46 are pending.

Applicant earnestly and respectfully requests the Office to reconsider its assertion of *prima facie* obviousness and to allow the pending amended claims. Should this paper not result in a Notice of Allowance, Applicant respectfully requests that the Examiner contact the undersigned at 650-849-6611 to arrange for an interview.

If there is any further fee due in connection with the filing of this Amendment, please charge the fee to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

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By: Elisabeth Barek
Elisabeth Jaffe Barek
Reg. No. 46,797
Customer No. 22,852